FDA Oversight of Cell Therapy Clinical Trials

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FDA Organization

- Office of the Commissioner
  - Office of Combination Products
- CBER (Center for Biologics Evaluation and Research): vaccines, blood and blood products, human tissue/tissue products for transplantation, cell therapy, gene therapy, donor screening tests for blood and tissue safety, devices
- CDRH (Center for Devices and Radiological Health): devices for treatment, implants, diagnostic devices
- CDER (Center for Drug Evaluation and Research): drugs, monoclonal antibodies, therapeutic proteins)
- CVM
- CFSAN
- NCTR

CBER Organization

- Immediate Office of Director
- Office of Blood Research and Review
- **Office of Cellular, Tissue and Gene Therapies**
- Office of Vaccines Research and Review
- Office of Compliance and Biological Quality
- Office of Biostatistics and Epidemiology
- Office of Communication, Training and Manufacturers Assistance
- Office of Management

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OCTGT Products

- Cellular therapies
- Tumor vaccines and immunotherapy
- Gene therapies
- Tissue and tissue based products
- Xenotransplantation products
- Combination products
- Devices used for cells/tissues
- Donor screening tests (for use with cadaveric blood samples)

The "Tissue Rules"
(21 CFR 1271, Effective May 25, 2005)

Tissue Rule	Issues Addressed
Establishment Registration and Listing	Applicability: types and uses of products that will be regulated by these rules; requirements for registering and listing products
Donor Eligibility	Requirements for donor screening and testing for "relevant communicable disease agents and diseases"
Current Good Tissue Practice (CGTP)	Manufacturing to ensure that HCT/Ps do not contain communicable disease agents; reporting; inspections

21 CFR Part 1271

- These three rules form the platform for regulation of all human cells, tissues, and cellular and tissue-based products (HCT/Ps)
- For certain HCT/Ps ("361 HCT/Ps"), these regulations comprise the sole regulatory requirements
- For HCT/Ps regulated as drugs, devices, and/or biological products, the new tissue regulations supplement other requirements (GMP, QSR)

Premarket Review Pathways

- Biologics Regulations
  - IND – Investigational New Drug
  - BLA- Biologics License Application
- Device Regulations
  - IDE- Investigational Device Exemption
  - PMA- Premarketing Application
  - HDE- Humanitarian Device Exemption
  - 510k/De Novo
- Combination products
  - Pathway determined: Primary mode of action- RFD process (Office of Combination Products)
  - Previous intercenter agreements and precedents

Stem Cell-Based Products

- Fit regulatory definitions of the following:
  - Human cells, tissues, or cellular and tissue based products (HCT/P) (21 CFR 1271.3(d))
  - Biologics (PHS Act)
  - Drugs (FDC Act)
  - Cell therapy
  - Gene therapy- when genetic material is transferred to cells ex vivo

Evolution of Stem Cell Field

- Cell therapy and gene therapy products –and therefore stem cell products-- do not lend themselves to a “one size fits all” concept of product development and regulation
- Regulations set framework of criteria that must be fulfilled: safety, identity, purity, potency, and clinical efficacy
- Flexibility in how to fulfill the criteria

Examples of Safety Concerns for Stem Cells

- Defining the intended mode of action
- Characterization of the product, including potency
- Cell differentiation to undesired cell types
- Cell migration/trafficking to nontarget site(s)
- Potential uncontrolled cell proliferation or tumorigenicity
- Immunogenicity
- Graft-vs-host effects
- Interactions with devices, other tissues or drugs in vivo
- For gene-modified cells
  - Potential uncontrolled biological activity of the transgene
  - Alteration of expression of the nontransgenes
  - Insertional mutagenesis

FDA Review Team

REVIEW OFFICE	CBER	FDA	OUTSIDE CONSULTANT
Review Decision	Product Quality	Scientific Expert	Patient Advocate
Project Manager	Epidemiology	Product expert	Scientific Expert (SGE)
Pharm/Tox	Statistics	Clinical specialist	Advisory Committee
Clinical	Compliance	Methodology expert	
CMC		Policy Expert	
		Orphan products	
		Ethicist	
		Animal rule	
Basic Review Team	*Extended Review Team*	*Potential Consults or Collaborators*	*Potential Consults*

Examples of CMC Issues

- Controls to prevent transmission of infection from the donor or introduction of infectious agents during cell processing

  Donor Testing and screening for relevant communicable diseases
  - Autologous donors recommended but not required
  - Allogeneic donors must comply with 21 CFR 1271 Subpart C
    - HCT/P donor screening is medical history interview, physical assessment and medical record review
    - HCT/P donors are tested using FDA approved or cleared donor screening tests
- Cell banks- adventitious agent testing & characterization
- If mouse feeder layers used- test for the presence of murine viruses (and is a xenotransplantation product)
- Components, reagents, materials qualification

Examples of CMC Issues- 2

- Account for and control donor to donor variability
- Intrinsic safety concerns, based on cell source or history
- Adequate characterization of the product
  - Identity, purity, potency
  - Additional characterization
- System for product tracking and labeling
  - critical for patient specific products
- Stability of product and or cell line
  - number of passages/ doublings over time
  - maintain desired differentiation properties
  - karyotypic alterations
- Product comparability for manufacturing changes

Examples of Preclinical Issues

- Scientific basis for conducting clinical trial
- Data to recommend initial safe dose & dose escalation scheme in humans
- Proof of Concept Studies in relevant animal models
- Toxicology Studies in relevant animal species
  - Identify, characterize, quantify the potential local and systemic toxicities

Examples of Clinical Issues

- Collection procedure
  - Standard medical practice? Special instrument or kit?
- Optimal dose and administration
  - Starting dose level/dose escalation scheme
  - Route of administration
  - Dose schedule
- Define appropriate patient population
- If immunosuppression will be used:
  - Is the dose-schedule justified?
  - Long-term vs short term
  - Single drug vs a combination regimen
- Safety Monitoring plans
- Safety Reporting requirements
- Pediatric issues

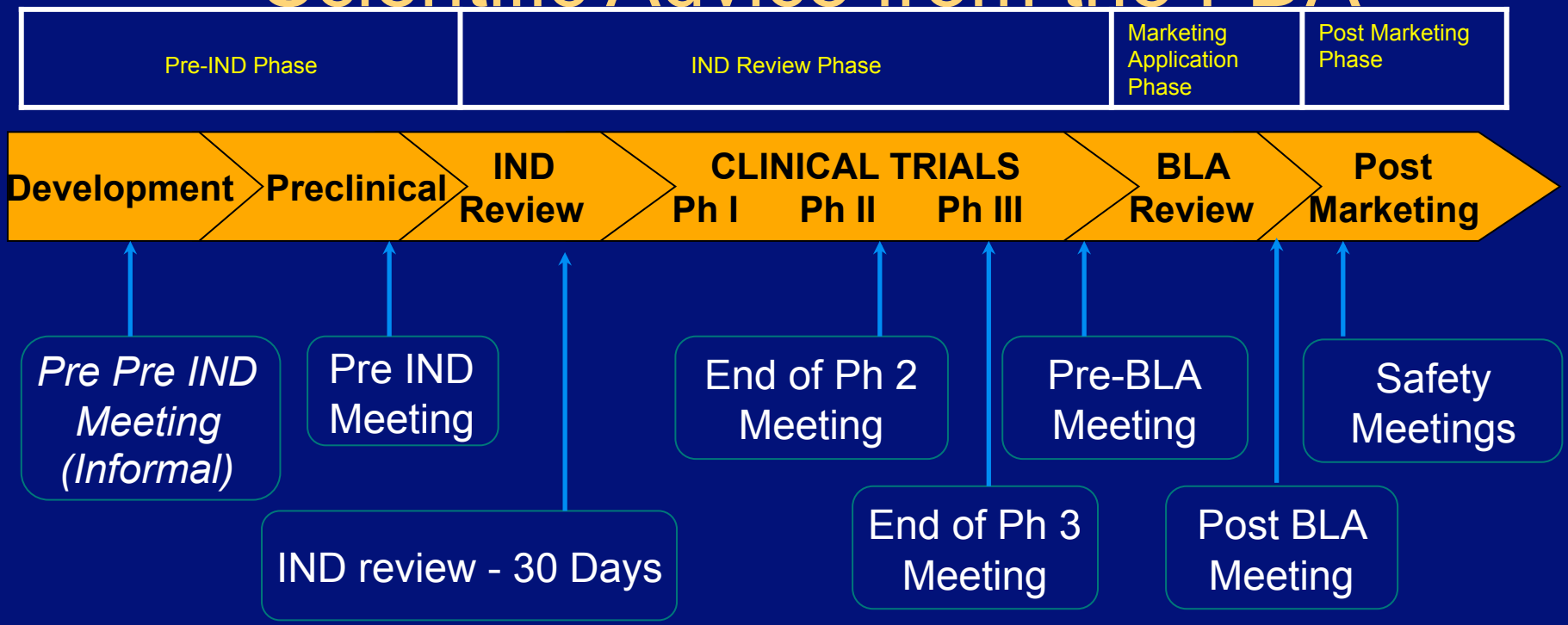
Administration of Stem Cell Products

- Delivery of stem cells to certain anatomic locations may require novel procedures and/or novel delivery devices
  - This needs to be considered early
- Cells delivered by certain devices (i.e. catheter) will be a Combination Product
  - Cells under Biologics/Drug regulations and Device under Device regulations (see 21 CFR 3.2(e))
  - Early consultation with FDA, and Device manufacturer, about regulatory aspects
- Compatibility of cells with the device
- Preclinical testing of cells and device
- Delivery procedure used during clinical trial and beyond
  - Training of clinical investigators

Outstanding Needs for the Field

- Standardized reporting/publication of results
- Technology to enable validated assays for enhanced product characterization and testing
- Biologically relevant animal species/models that will provide useful information about safety of the product
- Technology to assess biodistribution and fate of the product in patients
- Data regarding optimal timing and methods for stem cell delivery

Scientific Advice from the FDA



- Provide advice in response to specific queries
- In person or by teleconference
- Written minutes for formal meetings
- No fee

CBER Outreach to Stakeholders

- Advisory Committees
- Regulations
- Guidance Documents
- Standards Activities
- Workshops
- Liaison Meetings
- International Harmonization

Public Discussions of the Issues

- Nov 9 2009 NIH/JDRF/FDA Workshop: Next Generation Beta-Cell Transplantation
- Oct 27 2009 FDA/NCI Workshop: Therapeutic Cancer Vaccines Considerations for Early Phase Clinical Trials Based on Lessons Learned from Phase III
- May 14 2009 CTGTAC: Animal Models for Porcine Xenotransplantation Products Intended to Treat Type 1 Diabetes or Acute Liver Failure
- May 15 2009 CTGTAC: Products Intended to Repair or Replace Knee Cartilage
- Mar 13 2009 FDA/NIH/CIBMTR/ASBMT Workshop: Clinical Trials Endpoints for Acute Graft-Versus-Host Disease After Allogeneic Hematopoietic Stem Cell Transplantation
- April 10 2008 CTGTAC: Safety of Cell Therapies Derived from Human Embryonic Stem Cells
- Topics prior to 2008:
  - Cellular Replacement Therapies for Neurological Disorders
  - Placental/Umbilical Cord Blood For Hematopoietic Reconstitution
  - Allogeneic Pancreatic Islets for Type 1 Diabetes
  - Cellular Products for the Treatment of Cardiac Disease
  - Cellular Products for Joint Surface Repair
  - In Vitro Analyses of Cell/Scaffold Products
  - Insertional Mutagenesis by Retroviral Vectors

Use of Consensus Standards by Federal Agencies

- Codified in the National Technology Transfer and Advancement Act of 1995
  - Implementation defined by FDA Policy
- Standards may be referred to in FDA Guidance and Regulation

Potential Benefits of Standards Use

- Facilitate the development and maintenance of guidance
- Address issues not covered by FDA Guidance
- Facilitate product design
- Improve time to market
- Leverage industry efforts
- May lead to international harmonization

Standards Examples:

- ASTM F2386 Standard Guide for the Preservation of Tissue Engineered Products
- ASTM F2383 Standard Guide for Assessment of Adventitious Agents in Tissue Engineered Products
- ASTM F2315 Standard Guide for Immobilization or Encapsulation of Living Cells or Tissue in Alginate Gels
- ATCC ASN-0002 Authentication of Human Cell Lines: Standardization of STR Profiling*
- AMII/ISO 13022 Tissue Safety*
- ISO 11238 Identification of Medicinal Products Structures and Controlled Vocabularies for Substances and Ingredients*

International Engagements

- As an emerging product area, cell and gene therapies are prime area for prospective harmonization and convergence of regulatory approaches
  - International Conference on Harmonisation (ICH)
  - FDA-EMEA ATMP “Cluster”
  - Regulatory exchanges

ICH Gene Therapy Discussion Group (GTDG)

- Monitor emerging scientific issues
- Proactively set out principles that may have a beneficial impact on harmonization
- Ensure that the outcomes of the GTDG are well understood and widely disseminated
  - Public ICH web page
    - http://www.ich.org/
  - Public communications papers
  - Public press statements from the ICH SC
  - Public ICH workshops

Published ICH Considerations

- **General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors, 10/2006**
- **Oncolytic Viruses, 11/2008**
- **Viral/Vector Shedding, 6/2009**

FDA-EMEA ATMP "Cluster"

- Formal cooperation and confidentiality arrangement between FDA and European Medicines Agency (EMEA) for pharmaceuticals initiated 9/03; extended 9/05 to 9/2010
- Over time, "clusters" of specific areas of interest were developed for more targeted information exchanges
- With EMEA product scope enlargement to include tissue engineering with cell and gene therapies ("advanced therapeutic medicinal products" – ATMPs), ATMP "cluster" initiated 2008

FDA-EMEA ATMP "Cluster"

- Regular teleconferences to share thinking on regulatory approaches, both general and specific issues
- Information sharing on draft documents
- Engage reciprocally in workshops and advisory committees, working parties

Regulatory Exchanges

- OCTGT has hosted on limited basis regulatory colleagues, Fall of 2009:
  - EMEA ATMP expert
  - Japan Pharmaceutical and Medical Device Agency (PMDA) cell therapy expert
  - Additional exchanges planned for Fall of 2010
- OCTGT experts routinely respond to foreign regulatory inquiries, calls for assistance, both through written communication, face-to-face exchanges, presentations at international fora

Contact Information

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